In The United States Patent Office

In re Application of Pravin M. PATEL, *Stabilized Steroid Composition And Method for Its Preparation*

Serial No.: 10/762,652
Filing Date: 22 January 2004

DECLARATION UNDER 37 C.F.R. § 1.132

I, Pravin Patel, hereby make this Declaration under 37 Code of Federal Regulations § 1.132.

1) I am the inventor of the captioned patent application. I respectfully believe that my academic training and professional experience qualify me as one of skill in the art of pharmaceutical formulation science. I attach a copy of my *curriculum vitae* summarizing my academic training and professional experience.

2) One of skill in the art would understand that linoleic acid is an omega-6 acid. One of skill in the art would understand that safflower oil contains approximately 78% linoleic acid. The captioned patent application, however, refers to linoleic acid as an "omega-3 acid" and refers to safflower oil as a source of "omega-3 acid." This is a typographical

error. One of skill in the art would, on reading the captioned patent application, understand that the reference to linoleic acid and safflower oil is a reference to "omega-6," rather than to an "omega-3," acid.

3) I have read and understand the prior art of record, including Mark W. GRINSTAFF *et al., Methods for In Vivo Delivery…*, United States Letters Patent No. 5,560,156 combined with John E. HOOVER *et al., Remington's Pharmaceutical Sciences* pp. 956-71 (18th ed., 1990).

4) Hydrocortisone 17-butyrate is a topical steroidal anti-inflammatory agent. It is used topically. It is commercially available in The United States as a topical cream, a topical lotion, a topical ointment, and a topical solution.

5) Grinstaff teaches to make polymer micro spheres. Grinstaff teaches that these micro spheres may be made with hemoglobin or with other proteins such as albumin.

6) When made with hemoglobin, Grinstaff teaches that these micro spheres are useful as a blood substitute.

7) When the micro spheres are made with other proteins, Grinstaff teaches that these micro spheres may be useful for intravenous delivery of imaging agents or therapeutic compounds: Grinstaff at 26:6-31 teaches that his micro spheres may be filled with cytotoxic drugs, non-steroidal anti-inflammatory agents, steroids, and / or immunosuppressive agents.

8) Grinstaff *at e.g.*, 26:21-31; 26:45-51, enumerates many drugs potentially suitable for inclusion in the interior fill of his synthetic blood micro spheres. Grinstaff, however, fails to mention hydrocortisone 17-butyrate.

9) This is not surprising because hydrocortisone 17-butyrate is not recognized in the art as being acceptable for intravenous administration. Thus, an artisan of skill in the art to which Grinstaff pertains would therefore not consider hydrocortisone 17-butyrate suitable for inclusion in Grinstaff's intravenous micro spheres.

10) Grinstaff teaches that the imaging agent or therapeutic agent included in the micro sphere may be dissolved in a "biocompatible oil." Grinstaff teaches that fluorocarbons, soybean oil, safflower oil, coconut oil, olive oil, cotton seed oil and any other biocompatible oil are suitable.

11) Grinstaff, however, fails to teach that the fluorocarbon or biocompatible oil must contain omega-6 acid. To the contrary, Grinstaff teaches to use several oils which do not contain omega-6 acid. For example, Grinstaff teaches one of skill in the art to use fluorocarbons; fluorocarbons do not contain omega-6 acid, so this teaching would lead one of skill away from my invention. Similarly, Grinstaff teaches to use coconut oil; cocoanut oil does not contain omega-6 acid, so this teaching would lead one of skill away from my invention.

12) Grinstaff also fails to mention that the bio-compatible oil must contain omega-6 acid in an amount sufficient to stabilize hydrocortisone 17-butyrate. For example, Grinstaff teaches to use olive oil. Olive oil is up to 83% oleic acid, an omega-9 acid, and up to 20% palmitic acid. No evidence of record shows that olive oil contains omega-6 acid in an amount sufficient to stabilize hydrocortisone 17-butyrate.

13) Hydrocortisone is not interchangeable with hydrocortisone 17-butyrate. For example, hydrocortisone 17-butyrate is approved only for topical administration. In contrast, hydrocortisone is approved for systemic administration as an intramuscular injection, as an enema and as an oral dosage. *See* Hoover at 965. The art of record cautions that while hydrocortisone may also be administered topically, "Systemic side effects can result from topical application." *Id.*

14) Similarly, hydrocortisone 17-butyrate degrades to hydrocortisone 21-butyrate. No evidence shows that hydrocortisone degrades into hydrocortisone 21-butyrate. Hydrocortisone lacks a butyrate moiety. Hydrocortisone would therefore not be expected to degrade into hydrocortisone 21-butyrate, nor into any other butyrate form.

15) The claimed invention shows how to stabilize a topical drug. In contrast, Grinstaff teaches micro spheres suitable for intravenous

administration. One of skill in these two arts would not consider these two fields the same. Further, one of skill in the art would not consider Grinstaff's blood substitute technology "reasonably pertinent" when formulating eczema drugs.

16) Grinstaff teaches that his micro spheres are admirably stable. Grinstaff, at 34:53 to 35:22, notes that at body temperature, his micro spheres survive intact for at least a month. Grinstaff, at 38:5-36, teaches that to liberate drug contained in the micro spheres, one must dissolve the micro spheres with an organic solvent (Grinstaff uses mercaptoethanol). Grinstaff thus teaches that when a drug or medical imaging agent is included in his micro spheres, the spheres survive intact for at least a month before opening and releasing the drug.

17) This may be quite advantageous when administering a medical imaging agent. This would, however, render a topical medicine like hydrocortisone 17-butyrate inoperable. Adding hydrocortisone 17-butyrate to Grinstaff's micro spheres would sequester the hydrocortisone 17-butyrate, rendering it unavailable and ineffective.

18) Further, Grinstaff teaches that the micro spheres would sequester the hydrocortisone 17-butyrate for at least a month. Hydrocortisone 17-butyrate, however, is administered *topically*; thus, if the patient bathes at

least once a month (a likely assumption for a patient who has access to prescription drugs such as hydrocortisone 17-butyrate) the patient would wash away the intact micro spheres - and their drug load - before the drug is released.

19) A patient could conceivably open the micro spheres by washing the micro sphere-treated skin with an organic solvent such as mercaptoethanol. This would be counter-productive, however, because organic solvent dries and damages skin. Compounding the problem, hydrocortisone 17-butyrate is used to treat eczema - already sensitive skin - so washing eczema-affected skin with an organic solvent would *exacerbate* the eczema, not ameliorate it.

20) Grinstaff (alone or combined with Hoover) does not enable one of skill in the art to practice the claimed invention. This is for several reasons. First, Grinstaff teaches to encapsulate the fill material in a micro sphere. Encapsulating hydrocortisone 17-butyrate, however, would render it inactive.

21) Second, Grinstaff provides a laundry list of bio-compatible oils. Grinstaff, however, does nothing to guide the artisan towards the operable species and away from inoperable species. To the contrary, Grinstaff teaches that all these oils are interchangeable. Reading Grinstaff, an

artisan would be as likely (or indeed, be more likely) to make an inoperable (non-stabilized) formulation as an operable (stabilized) formulation.

22) The prior art teaches that hydrocortisone 17-butyrate degrades into hydrocortisone 21-butyrate. Nothing in the prior art of record contradicts this. Thus, one of skill in the art would have expected that hydrocortisone 17-butyrate, whether or not incorporated into Grinstaff's micro spheres, would degrade into the 21-butyrate form.

23) In contrast to what the prior art teaches, I have found a way to stabilize hydrocortisone 17-butyrate. The instant Specification shows that after 6 months of storage at 40° C, an eczema skin drug made without added omega-6 acid has **9.17%** total impurities (6.36 % hydrocortisone 21-butyrate and 2.81% other impurities). In contrast, the same topical drug product with added omega-6 acid has only **5.56%** total impurities (5.00 % hydrocortisone 21-butyrate and 0.56% other impurities).

24) These results are of both statistical and practical significance. These results are statistically significant because the superior results shown in the instant patent application are not likely to be caused by random variation in the data. These results are practically significant

because, as the Specification explains at 2:12-14, isomerization is of particular concern to pharmaceutical formulators since the isomerization reaction raises therapeutic and regulatory issues regarding the efficacy and composition of isomerized compositions.

25) I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

Signature : Pravin M. Patel
Name : Pravin Patel
Dated as of : January 07, 2008

Attachments
Curriculum vitae.

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PRAVIN M. PATEL
2045 Bordeaux St
West Bloomfield, MI 48323
(248) 862-2184 (Res.) , (248) 760-7537 (Cell)

Career Objective :
Administration of Pharmaceutical Manufacturing or Product Development Operation.

Pharmaceutical Experience : 34 years of diversified experience working in Pharmaceutical Manufacturing, Quality Control, Regulatory Affairs, Product Development and Business Development. I was the member of the senior management team and a member of Board of Directors during my 33+ years of employment at Ferndale Laboratories Inc.

Positions Held :

Ferndale Laboratories Inc. (Ethical Pharmaceuticals since 1897), Ferndale, MI 48220. 1972 to Oct. 2005

Vice President, Scientific Affairs 2000 to Oct 2005
Ferndale Laboratories Inc. (Ethical Pharmaceuticals since 1897), Ferndale, MI 48220.

Ferndale Laboratories specializes primarily in the manufacturing and distribution of the skin and would care prescription and over the counter or medical device products. Topical products are indicated for the treatment of Inflammation, Dermatitis, Itching, Acne, Oily skin, Dry skin and Hemorrhoids. Wound care products are surgical adhesive and adhesive remover for wound dressings. In addition to skin care and wound care products, prior to 1995 Ferndale Laboratories manufactured and distributed Oral Solids and Liquid dosages containing Anti-Histamines, Nasal Decongestant, Expectorant, Cough suppressant, Analgesics, Appetite suppressants, Muscle relaxant and Antispasmodics.

Primary Functions :

- Responsible for Product Development and Analytical Methods Development department. I was responsible to guide four scientists (MS and PhD level)and one technician in the Product Development department . I was also responsible to guide Director of Analytical Methods Development who had 8-10 BS/MS and PhD level chemists. I Provided Technical Assistance to Manufacturing operation, Process validation group, Quality Control/Quality Assurance group, Regulatory Affairs group and Business development/Project Management group.
- Manage multiple Product development projects consisting of Formulation and Process development and scale-up for New Products. Technology transfer for products licensed from outside. Improve manufacturing process(es) for existing products

- Provide CMC information for filing IND, NDA or ANDA. Participate in the PreIND, IND or PreNDA meeting with FDA.
- Member of the New Products Committee to review Opportunities for developing products in-house or Licensing products from outside.
- Member of Senior Management team responsible for reviewing and instituting policies to ensure company-wide compliance with local, state and federal regulations.
- Review Master production Records, various SOPs, Raw material and finished product specifications, Process validation Protocols and reports, Cleaning Validation Protocols and reports, Deviation reports, Out-of-Specification investigation report and Annual Products Review reports.
- Manage pilot Manufacturing plant.
- Responsible for providing 24 hour medical information, to consumers, Pharmacists or medical personnel, for marketed products.
- Member of Product Corrective Action Committee responsible for Product recall.
- Responsible for submitting departmental budget.
- Provide technical support to Sales and Marketing personnel.
- Attend major Dermatology and Clon Rectal Surgeon conventions.
- Attend Scientific and Trade meetings e.g. AAPS, APhA and BPA
- Member of the Board of Directors.

Vice President, Business Development and Project Management 1994 to 1999

Primary Functions:

- Responsible for Product Development and Project Management.
- Review New products opportunities.
- Interact with Business partners.
- Member of Senior management team, New Products Committee and Product Corrective Action Committee.
- Review Master Production Records and SOPs
- Interact with Manufacturing, Quality Control/Quality Assurance and Regulatory Affairs for overall compliance with local, State and Federal Regulations.
- Provide technical support to Sales and Marketing personnel.
- Review and recommend new equipment purchases.

Vice President, Operations (Laboratories) 1988 to 1993

Primary Functions:

- Responsible for Quality Control, Manufacturing, Product Development and regulatory Affairs.
- Responsible for issuing and enforcing policies to ensure company-wide compliance with local, state and federal regulations.

- Prepare Master Production Records, Product Specifications, Raw materials and Packaging component specifications.
- Review Batch Records and approve for final release to distribution.
- Maintain Stability testing program.
- Maintain Calibration and Preventive Maintenance program for Quality Control and Manufacturing departments.
- Observe cGMP compliance throughout the facility.
- Manage contract manufacturing business..
- Maintain annual Establishment registration and product listing with FDA
- Primary point of contact during the audit of the facility and for correspondence with regulatory agencies e.g. FDA, DEA, OSHA etc.
- File ANDAs, ANDA supplements and ANDA annual reports.
- Maintain customer complaint files. File adverse drug experience (ADE) reports for ANDA products.
- Review and approve labeling and promotional material for regulatory compliance.
- Principal coordinator for market withdrawal/recall of products.
- Attend Scientific and Trade meetings e.g. AAPS, NPA, AAD etc.
- Responsible for providing 24 hr medical information to Medical personnel, Pharmacists and consumers for marketed products.
- Responsible for purchasing new Manufacturing and Packaging machinery.
- Member of senior management team and member of the Board of Directors.

Director of Quality Control and Technical Services **1976 to 1987**

Primary Functions:

My responsibilities were same as mentioned above (as Vice President of Operations) except I was not a member of the Board of Directors.

Director of Quality Control **1973 to 1975**

Primary Functions:

- Responsible for the operation of Quality Control Laboratories.
- Testing of Raw Materials and Finished Products.
- Writing Raw material and finished product Specifications.
- Develop test methods for non compendial products.
- Maintain Stability testing program.
- Review Master Production Records.
- Review finished Batch Records for the final release of the products
- Observe cGMP compliance through out the facility.
- Principal coordinator for FDA, DEA and ATF audits. Respond to issues raised during the audit.

Quality Control Chemist **April 1972 to Dec. 1972**

Primary Functions:

- Quality control testing of Raw Materials and Finished Products

Supervisory Pharmacist **June 68 to Sept. 1969**
Squibb of India, Baroda, India

Primary Functions:

- Supervise Tablet granulation department (15 employees)

Education:

Bachelor of Pharmacy	Gujarat University, Ahmedabad, India	1968
M.S. Pharmacy	Wayne State University, Detroit, MI 48202	1972

Professional License:

Registered Pharmacist	State of New York and State of Michigan

Training Courses:

- Process Analytic Technology Training, SWE Enterprises Inc.
- Emulsion-Suspension Technology, The center for Professional Advancement
- Skin Product Development, The Institute for Applied Pharmaceutical Sciences
- How to Manage Multiple Projects, Meet Deadlines and Achieve Objectives, Fred Pryor Seminars.
- Strategic Project Management, The University of Michigan, Dearborn Center for Corporate and Professional Development
- Introduction to Rheology Training Program
- An overview of Good Manufacturing Practice, GMP Institute Inc.
- Microsoft Word and Excel, Comp USA
- Attended several technical seminars offered by PhRMA, NPA, FDA, DEA and AAPS

U.S.Patent:

Composition and method for the treatment of Anorectal disorders,
US Patent #6,833,139 B1, Dec. 21, 2004.

Stabilized steroid composition and method for its preparation, US Patent application Serial No. 10/762,652. (Patent application is being examined).
Composition and method for dermatological treatment, US Patent application serial No. 10/425,359. (Patent application is being examined).

Hobbies: Golf, Tennis Reading and Music.